REMARKS

Amendments to the Specification

Applicants have amended the specification to incorporate by reference the substitute Sequence Listing, filed concurrently herewith via EFS. Support for the substitute Sequence Listing is found throughout the specification as filed, for example in paragraphs [0071] and in Figure 1C as originally filed. No new matter is introduced by way of this amendment; its entry is respectfully requested.

The Listing of Claims

Applicants have not amended the claims herein, but include the Listing of Claims for completeness.

The Notice of Panel Decision from Pre-Appeal Brief Review and the Interview Summary

The Notice, mailed on June 1, 2007, has indicated that a Pre-Appeal Brief conference had been held, but that the application remained under appeal because there is at least one actual issue for appeal. The panel has determined the status of the claims as follows:

Claims allowed: none

Claims objected to: none

Claims rejected: 4-5, 12, 43-44.

A telephonic interview was conducted between Examiner Haddad and the undersigned on May 30, 2007, and an Interview Summary was mailed on June 1, 2007. In accordance with § 713.04 of the MPEP, Applicants set forth the substance of the interview as follows: The Examiner indicated that the rejections were still maintained and that only claim 4(i) would be allowed. No agreement was reached with respect to the rejected claims.

The Substitute Sequence Listing

Applicants submit this substitute sequence listing to correct an error in the specification as filed.

SEQ ID NO:6 is the amino acid sequence of human WARP, and is shown in Fig. 1C in an alignment with mouse WARP. The human WARP amino acid sequence is also disclosed in SEQ ID NO:6. Both the WARP sequence disclosed in Fig. 1C and in SEQ ID NO:6 disclose an aspartic acid residue at position 211 ("D211" or "Asp211") (*see, e.g.*, in Fig. 1C, fourth line of human sequence, in the sequence GSILDARMPQQ", D211 is underlined). The same amino acid residue is disclosed in SEQ ID NO:6 as filed.

The specification discloses that SEQ ID NO:6 is encoded by SEQ ID NO:5. *See*, paragraph [0071] of the instant specification ("The cDNA encoding WARP and its corresponding amino acid sequence are represented in SEQ ID NOS: 5 and 6, respectively."); *see* also, Example 15 and paragraph [0153] ("The nucleotide sequence (SEQ ID NO:5) and its corresponding amino acid sequence (SEQ ID NO:6) are shown in Figure 6.") Because SEQ ID NO:6 is encoded by SEQ ID NO:5, the presence of D211 in SEQ ID NO:6 necessarily requires the presence of D211 in SEQ ID NO:5.

SEQ ID NO:5 as filed included an error in that the codon that encodes D211 was missing at nucleotide position 331 (spanning from nucleotides 331-333). This error resulted in one amino acid—D211—missing from the translation of SEQ ID NO:5 as compared to the amino acid sequence of SEQ ID NO:6. D211 may be encoded by two codons, GAT or GAC. At the position corresponding to D211, SEQ ID NO:5 as corrected in the substitute sequence listing provided herewith, now recites "GAY". "Y" refers to and is the international symbol for pyrimidine, of which T and C are. Thus, "GAY" can mean GAT or GAC, both of which code for aspartic acid. *See*, also "Table 1: List of Nucleotides" in M.P.E.P. 2422.

In view of the above, Applicants submit that the substitute sequence listing merely corrects an error in the specification that, if left uncorrected, would lead to an error in any patent that issued from the application. Because human WARP includes D211 as filed, both in

the figures and in the sequence listing, and because SEQ ID NO:6 is encoded by SEQ ID NO:5, correcting the error in SEQ ID NO:5 does not add new matter.

Summary of The Final Office Action

The Rejections Under 35 U.S.C. § 112 First Paragraph

The Claims Are Enabled

The final Office Action dated December 21, 2006, has maintained the rejection of claims 4-5, 12 and 43-44 under 35 U.S.C. § 112, 1st paragraph, contending that, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well-established utility, one skilled in the art would not know how to make and use the claimed invention, for the reasons set forth in the Office Action mailed March 31, 2006. The Office Action further contends that, among other things, the specification does not provide sufficient guidance as to the nature of the changes made to a reference WARP sequence for the skilled artisan to make and use such "derivative" and "homolog." In Applicants' response to the final Office Action, Applicants amended claim 4 to delete the phrase "or a derivative or homolog thereof which in situ forms part of the extracellular matrix (ECM) in an animal." Applicants respectfully traverse this rejection.

With respect to the contention of the Office Action that the claims lack a specific and substantial utility, Applicants note: the claims do not recite the use of a polypeptide of the invention as a marker for ECM integrity. Thus, a showing of the correlation of WARP with ECM integrity is not necessary. Nonetheless, the polypeptide of the instant invention has a substantial and specific utility as a histological marker. For example, as disclosed in paragraph [0002] of the specification, which published as U.S. Patent Publication No. 20040214349 ("the '349 publication") "the present invention provides a molecular marker of cartilage integrity. The *identification of the molecular marker in circulatory or tissue fluid is indicative of disrepair of the extracellular matrix and in particular cartilage* such as caused or facilitated by trauma or a degenerative disease or other condition, for example, arthritis or autoimmunity, specifically, a histological marker for cartilage" (emphasis added).

Further, as disclosed in paragraph [0022] of the '349 publication, "the identification of WARP permits the detection of mutations in WARP such as those involved in disease conditions such as cartilage disease or arthritis or in a propensity for the development of disease conditions. WARP expression may also be a sensitive indicator of cartilage cell differentiation and is proposed to be useful in monitoring repair, regeneration or other disease processes in a subject. Furthermore, WARP may be used to condition or stabilize stem cells in order to facilitate imprinting of stem cells for tissue replacement therapy."

Paragraph [0007] of the '349 publication discloses that "both WARP and *WARP* represent molecular markers of ECM and in particular cartilage integrity. The presence or absence of WARP or altered levels of WARP relative to normal controls is proposed to be indicative of disease conditions such as arthritis or cartilage disease." The specification further discloses that a loss of ECM integrity can be detected "by screening body fluid from the animal for the presence of a WARP fragment thereof wherein the presence of the WARP or fragment is indicative of a loss of ECM integrity. *See* also paragraph [0022] of the '349 publication ("the identification of WARP permits the detection of mutations in WARP such as those involved in disease conditions such as cartilage disease or arthritis or in a propensity for the development of disease conditions. WARP expression may also be a sensitive indicator of cartilage cell differentiation and is proposed to be useful in monitoring repair, regeneration or other disease processes in a subject. Furthermore, WARP may be used to condition or stabilize stem cells in order to facilitate imprinting of stem cells for tissue replacement therapy.").

Applicants submit that detecting WARP in circulating or tissue fluid is a clear indication of disrepair of the ECM. Moreover, the specification discloses how to detect WARP expression, for instance by Western blot and Northern blot. *See*, for example, Figure 3, Examples 4 and 12, and paragraphs [0149], [0150] of the '349 publication, as discussed in Applicants' response filed March 21, 2007, pages 5-6.

Further, as disclosed in paragraph [0150] of the '349 publication, "expression experiments demonstrate that WARP mRNA is expressed highest in primary rib chondrocytes which contain a mixed population of resting, proliferative, maturing and hypertrophic chondrocytes and in MCT cells induced to express a hypertrophic chondrocyte-like phenotype

(Lefebvre et al., 1995, supra). WARP mRNA was undetected or expressed at very low levels in all other tissues and cell lines examined, including MCT cells induced to form osteoblast-like cells. Interestingly, WARP expression was down-regulated when rib chondrocytes were allowed to de-differentiate into fibroblast-like cells suggesting that expression is tightly controlled by the chondrocyte program of gene expression. This is supported by our finding that when MCT cells are induced to change from a hypertrophic-like to an osteoblast-like phenotype by changing the temperature of incubation from 37°C to 32°C, WARP expression was reduced approximately 6-fold (FIG. 3C)."

In addition, as discussed in the March 21, 2007 response, page 6, Figure 5 and Example 6 show that WARP forms higher-order structures in vivo. In particular, Western blot analysis shows that WARP is expressed in newborn mouse cartilage. "[T]he results clearly show that WARP is also found in the cartilage matrix in vivo, and the necessity for extraction with a chaotropic agent suggests that it may be a strongly interacting matrix component." See, paragraph [0154] of the '349 publication. The need for a chaotropic agent to extract WARP from the cartilage matrix in vivo strongly indicates that WARP is tightly bound or associated with the extracellular matrix. Thus, detecting WARP in a circulatory or tissue fluid—without the use of a chaotropic agent—is strongly indicative of matrix disrepair.

In view of the above remarks, Applicants submit that the specification provides support for the utility of WARP for identifying these cells using the WARP polypeptide of the instant invention. Moreover, based on the expression profile of WARP, Applicants respectfully submit that any number of specific and substantial utilities for WARP as described in the specification stem directly from its chondrocyte cell and cartilage tissue-specific expression profile. Applicants respectfully submit that the claimed invention is supported by at least a specific and substantial asserted utility such that one ordinarily skilled in the art would appreciate the diagnostic utilities of the WARP polypeptides and know how to use the claimed invention. Accordingly, Applicants respectfully request that the Examiner withdraw the rejections of claims 4-5, 12 and 43-44 under 35 U.S.C. § 112, first paragraph.

The Claims Satisfy The Written Description Requirement

The final Office Action has maintained the rejection of claims 4-5, 12 and 43-44 under 35 U.S.C. § 112, first paragraph as failing to meet the written description requirement, for the reasons made of record in the prior Office Action mailed March 31, 2006. The Office Action contends that there is no described or art-recognized correlation or relationship between the structure of the invention, the Willebrand domain of the WARP and its function in the ECM. Thus, the Office Action contends, that one of skill in the art would not envisage, based on the disclosure, the claimed genus or derivative, homolog, 95% or 99% similarity to SEQ ID NO:5, which retain the features essential to the present invention. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the specification provides ample support for the terms "95% homology" and "99% homology." The specification in paragraph [0051] of the '349 publication defines "homolog" as including "an analogous polypeptide having at least about 65% similar amino acid sequence from another animal species or from a different locus within the same species." Further, as disclosed in paragraph [0144] of the '349 publication, "[t]he human homolog of WARP was identified by searching the genome data with the mouse WARP protein sequence. A match with a predicted protein sequence (hypothetical protein FLJ22215) with very high homology to the mouse WARP was found. ... *These sequences are clearly homologs of each other because they share 79% amino acid identity (see FIG. 1C). In addition, if conserved changes are considered in the analysis, they share 95% identity*" (emphasis added).

Given that Applicants provide written description for "homolog" and a mouse and a human WARP sequence that are 79% identical, or 95% identical of conserved amino acids are considered, Applicants respectfully submit that the presently amended claims satisfy the written description requirement.

Applicants also respectfully disagree with the Office Action that an insufficient number of species is disclosed. Applicants disclose a human and a mouse WARP protein. Areas of sequence identity and similarity are shown in Figure 1C. Given that Applicants provide adequate written description for "homolog" and a mouse and a human WARP sequence that are

79% identical, or 95% identical of conserved amino acids are considered, Applicants respectfully submit that the presently amended claims satisfy the written description requirement. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejections of claims 4-5, 12 and 43-44 under 35 U.S.C. § 112, first paragraph.

Conclusion

Based on the above remarks and amendments, Applicants respectfully request a finding of allowance of claims 4, 5, 12 and 43-44. If the United States Patent and Trademark Office deems that an interview is appropriate, Applicants would appreciate the opportunity for such an interview. The Examiner is invited to contact the undersigned to discuss any outstanding matters that may be resolved by telephone.

In addition to the fee for the three-month extension of time to file this response, and the fee for the request for continued examination, Applicants believe that no additional fees are required. Should addition fees be required, or if fees are overpaid, the Director is hereby authorized to charge any required fees or credit any overpayments to Deposit Account 02-4377 of Baker Botts, LLP.

Respectfully submitted,

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